CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
MINERAL OIL & PETROLEUM OIL - **PARAFFIN HYDROCARBONS**

Chemical Code # 000401 & 1641, Tolerance # 00149
SB 950 # 754
Original date: 7/19/01

I. DATA GAP STATUS

Chronic, rat:	Data gap, no study on file
Chronic, dog:	Data gap, no study on file
Combined (chronic/onco), mouse:	Data gap, inadequate study, possible adverse effect indicated.
Oncogenicity, rat:	Data gap, inadequate study, possible adverse effect indicated.
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	Data gap, no study on file
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	Data gap, inadequate study, possible adverse effect indicated
Chromosomal aberration:	Data gap, inadequate study, no adverse effect indicated
DNA damage:	Data gap, no study on file
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

File name:T010719

Revised: M. Silva, 9/88; Kishiyama & Silva, 7/19/01.

These pages contain summaries only. Individual worksheets may contain additional effects.
Note: MRD compounds are described as paraffinic white oils.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

No study submitted

CHRONIC TOXICITY, RAT

Subchronic Study:

149 - 023 117136 "A Three Month Oral Toxicity Study of MRD-77-6, MRD-77-7, MRD-77-8, and MRD-77-9 in Rats," (Rinehart, W.E.; Bio/dynamics Inc., Project #: 77-1755; 9/1/77). MRD-77-6, MRD-77-7, MRD-77-8 and MRD-77-9 (paraffinic white oils) were fed in diet to Long-Evans rats (20/sex/dose) at 0, 300 and 1500 ppm for three months. Total leukocytes was increased significantly (148% and 140%) with MRD-77-7 (1500 ppm) and MRD-77-6 (300 ppm); and slightly increased (107 - 132%) with MRD-77-8 and MRD-77-9. NOEL > 1500 ppm (No toxicologically relevant effects from any compound to either sex.) UNACCEPTABLE (Report contains no information on the stability and characterization of test articles, no analysis of dosing material, no animal age or rationale for dose selection [two dose/test article], no GLP or QA sign-off and no MTD). (Kishiyama & Silva, 11/2/00).

CHRONIC TOXICITY, DOG

No study submitted

Subchronic Study:

149 - 024 117139 "A Three Month Oral Toxicity Study of MRD-77-6, MRD-77-7, MRD-77-8, and MRD-77-9 in Dogs," (Rinehart, W.E.; Bio/dynamics Inc., Project No. 77-1756; 9/1/77). MRD-77-6, MRD-77-7, MRD-77-8, and MRD-77-9 were fed in diet to Beagle dogs (4/sex/dose) at 0, 300 and 1500 ppm for three months. Increased frequency of soft stools, mucoidal and mucohemorragic fecal discharge and emesis was reported. Slight decrease in testes and increase in liver weight for males and reduced ovary weight for females were reported. UNACCEPTABLE (Report contains no information on the stability and characterization of test articles, no analyses of dosing materials and rationale for dose selection; only two doses/test article were used, no tabulated data on physical observations were presented, the actual health of the dogs is unknown during the study and no GLP or QA sign-off was included). Not upgradeable. (Kishiyama & Silva, 11/3/00).

ONCOGENICITY, RAT

149 - 017 117309 "Experiments to Create Cancer with Liquid Paraffin, Yellow Petrolatum and Wool Fat," (Schmähl, D., Reiter, A.; Published in: Arz. Forsch., 3:403-406;1953). Liquid paraffin was injected in 2.5 ml once subcutaneously and i.p. in a total dose of 9 ml/rat, divided over 15 individual injections in 40 weeks to BDI, BDIII and W rats (30 rats; strain not specified for each test). Another group was fed liquid paraffin (2% of diet) for 500 days (30 rats). Yellow vaseline was administered as 3 ml i.p. (8 rats) or 1 ml subcutaneously (26 rats). Wool fat was administered 1 ml i.p. + 1ml

subcutaneously at the same time (18 rats), once only. Male rats, after i.p. liquid paraffin injection, developed 3 malignant spindle-cell sarcomas (2 testicular & 1 abdominal) and 1 malignant myo-sarcoma. All rats had extensive abdominal growths and warts after i.p. liquid paraffin-injection. There were massive adhesions and spleen, liver or kidneys were surrounded by stiff, fatty membranes, accompanied by a yellow trans-sudation was in the abdomen. Paraffin inclusions occurred in liver and lymph glands. The report considered that liquid paraffin could not be considered "inactive." Vaseline induced 1 osteo-sarcoma near the i.p. injection site at day 658 (related to treatment) and a 2nd rat developed solid, whitish knots (spindle-cell granulation). Vaseline was in the subcutis as spherical cysts or in the abdominal cavity and was non-irritating. Wool fat induced heavy ascites a few hours after injection (5 rats died). The remaining rats had "heavy overgrowths" in the abdominal cavity, with chronic local irritating effects. Possible adverse effect: tumors from liquid paraffin and vaseline. These data are supplemental. (Kishiyama & Silva, 2/6/01).

ONCOGENICITY, MOUSE

149 - 017 117311 "The Carcinogenicity of New and Used Lubricants," (Agee, J., Barkley, W., LaDow, K., Rapien, I., Spalding, S., Stemmer, K.L., Suskind, R.R., Trosset, R.P.; Kettering Laboratory, University of Cincinnati, Cincinnati, OH; API Project #: PS-36; 7/83). Composite motor oil, 5 paraffinic base stocks (viscosities = 64, 133, 331, 485 & 990 SUS) and 2 napthenic base stocks (viscosities of 83 & 2008 SUS) each at 50 mg doses were applied dermally to interscapular skin of male C3H/HeJ mice (50/group) twice/week for 104 weeks. The number of animals with moderate epilation, together with crusty skin, was increased when treated with formulations containing toluene. Moderate epilation of the skin was observed on 4, 22, 24, 32, 36, 40, and 94% of animals treated with Used Composite Motor Oil, Paraffinic Oil 64 SUS, Paraffinic Oil 485 SUS, Paraffinic Oil 331 SUS, Paraffinic Oil 990 SUS, Paraffinic Oil 133 SUS and Napthenic Oil 83 SUS, respectively. Skin irritation was not observed on animals in the control (no treatment), Napthenic Oil 2008 SUS and New Composite Motor Oil groups. **The number of mice with tumors and skin irritation increased and the latent period for tumors decreased with used composite motor oil treatment.** UNACCEPTABLE. Not upgradeable (major deficiencies). These data are supplemental. (Kishiyama & Silva, 2/7/01).

149 - 020 117315 "Evaluation of the Dermal Carcinogenic Potential of Liquids Produced from the Cold Lake Heavy Oil Deposits of Northeast Alberta," (McKee, R.H., S.C. Lewis; Canadian Journal of Physiology and Pharmacology; 65:1793 - 1797 (1987)). Raw Bitumen (75% w/v suspension in toluene), Hycracking product (boils at 102-498 °C) and Go-Fining product (undiluted; boils at 259-519 °C) were applied dermally in 25 µl aliquots to the shaved backs of male C_3H/HeJ mice (50/group) 3 times/week until the mice died spontaneously, or until grossly diagnosed squamous cell carcinomas occurred (mice then sacrificed for humane reasons). Highly refined white oil was negative control. All mice were examined daily for appearance of dermal tumors and all received complete necropsies. **G0-Fining treatment decreased survival significantly and increased the incidence of tumors (papillomas progressing to malignancy) to 86% (median latency = 46 weeks). Crude Bitumen induced tumors in 26% of mice (median latency = 2 years).** Hycracking product showed no evidence of epidermal carcinogenicity. The report indicated that the results were predictable, based on previous dermal carcinogenic activity of products which distill at the temperatures of these products. Possible adverse effect indicated. These data are supplemental. (Kishiyama & Silva, 12/5/00).

149 – 020 117316 "Dermal Carcinogenic Activity of Petroleum-Derived Middle Distillate Fuels,"

(Biles, R.W., McKee, R.H., Lewis, S.C., Scala, R.A., DePass, L.R.; Bushy Run Research Center; Published in: Toxicology, 53:301 – 314 (1988)). The following compounds, origins and boiling ranges: virgin heating oil blending base (US 287-585 °F), lightly refined paraffinic oil (US 490-610 °F), commercial #2 heating oil from different sources (Middle East/Carribean Pool 383-705 °F; US 331-678 °F; Middle East 419-676 °F; Western Canadian 322-644 °F; Western Canadian/Venezuelan 313-666 °F, Western Canadian/Tar Sands 373-667 °F), Virgin heating oil blending base (sample 1) + catalytically cracked middle distillate (US 287-700 °F) and light catalytic cycle oil (US 640 °F) were applied in 25 µl aliquots to the clipped dorsal surface of male C3H/HeJ mice (40-50/group, 5/cage) 3 times/week for the lifetime of the mice or until all animals in the group developed carcinomas. Highly refined mineral oil was the negative control. The study was conducted over a 4-year period. . Animals were examined daily for dermal tumors and all mice received full necropsy at termination or death. The report states that carcinogenic potential of petroleum-derived materials is related to PAH content and that liquids that boil below PAH distillation range (700 °F) "would not be carcinogenic". Earlier studies supporting this conclusion were of short duration but recent studies with repeated application of petroleum-derived materials (middle distillate fuels 350-700 °F) produced tumors in mouse skin. The current study tested tumorigenic potential of a series of middle distillates, which varied with respect to boiling range, composition and source of blending stocks. Results with most samples showed low tumor yields (significantly increased over control), with long median latencies (by Weibull distribution function). Parameters examined did not affect tumorigenicity, as there were no apparent differences among treatment groups. Tumorigenic activity was not associated with PAH content and therefore was not PAH-dependent. There were also non-neoplastic dermal changes (hyperplasia) which may indicated preneoplasia. Possible adverse effect indicated. These data are supplemental. M. Silva, 12/6/00.

149 - 026 117143 "Dermal Oncogenicity Studies of MH-982, MH-983, MH-1140, MH-1141, MH-1142, MH-1143, MH-1144, MH-1171, MH-1176, and MH-1177 in Male C3H/HeJ Mice," (Hengler, W.C., De Pass, L.R.; Union Carbide, Bushy Run Research Center, Report #: 45-517; 7/7/83). MH-982 (positive control) at 10%, MH-983 (negative control), MH-1140 -1144, MH-1171, MH-1176 - 1177 at 100% were in 25 µl applied dermally 3 times/week (M, W, F) to male C3H/HeJ mice (50/group) from age 78 to 90 days until natural death occurred. The source(s) of the materials was not described. All positive control mice (MH-982) developed tumors and their survival time was reduced. **MH-1177 was reported as weakly carcinogenic.** Same samples (especially MH-1176 and MH-177) caused epidermal thickening hyperplasia and hyperkeratosis. UNACCEPTABLE (no analyses of dosing material, females not tested, no rationale for dose selection, no provisions described which prevented animals from licking/grooming treated skin, no clinical chemistry/hematology, incomplete necropsy, incomplete histopathology, no record of cumulative mortality). Note: Appendix II (Report # 45-518) includes data on 7 additional materials: MH-1183, -1184, -1185, -1186, -1187, -1188, and -1189 using 5% MH-982 as a positive control and the same basic protocol. Exposure to MH-1189 resulted in 5/50 papillomas, 7/50 carcinomas and 1/50 with both and was considered positive for skin oncogenicity. (Kishiyama & Silva, 11/21/00).

REPRODUCTION, RAT

No study submitted

TERATOLOGY, RAT

No study submitted

TERATOLOGY, RABBIT

No study submitted

GENE MUTATION

50667 001 037857 "In vitro Microbiological Mutagenicity Studies of Phillips Petroleum Company Hydrocarbons Propellants and Aerosols." (Stanford Research Institute, 5/13/77) Tested propellants A-17, A-31, A-108 and F plus aerosols D and E (See letter dated October 11, 1985 for components of A-31 and A-108 in 50667-001); tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation for 8 and 48 hours at 1 to 50% of the atmosphere above the plates in a dessicator; tested twice on separate days; methylene chloride as the positive control was not effective in TA1537 or TA1538; no increase in reversion rate reported; cytotoxicity by decrease of spontaneous reversion rate with aerosol D, aerosol E and propellant F at higher concentrations; UNACCEPTABLE (no description of propellants A-17 and F and aerosols D and E; no individual plate counts or number of plates per trial; positive control was not effective in two strains). JG, 10/28/87.

50667 001 037858 "Salmonella typhimurium Mammalian Microsome Plate Incorporation Assay - Soltrol 130 - Final Report." (Hazleton, 8/13/82). Isoparaffinic hydrocarbons (Soltrol 130), C10-C13 isoparaffins, "assumed 100%"; tested with strains TA 1535, TA1537, TA98 and TA 100 with and without rat liver activation, single trial with triplicate plates; 0, 41.2, 123.5, 370.4, 1111.1, 3333.3 or 10000 ug/plate; no increase in reversion rate reported; UNACCEPTABLE - single trial with no demonstration of cytotoxicity at highest concentration and no analysis of test article to demonstrate exposure of Salmonella. JG, 10/28/87.

50667 001 037859 "Mouse Lymphoma Forward Mutation Assay - Soltrol 130 - Final Report." (Hazleton, 8/2/82) Isoparaffinic hydrocarbons (Soltrol 130), C10-C13 isoparaffins, "assumed 100%"; tested with rat liver activation at 0, 83, 118, 168, 240 343, 490, 700 or 1000 ug/ml (1000 stated to limit of solubility) and without activation at 0, 8.3, 11.8, 16.8, 24.0, 34.3, 49, 70, or 100 mg/ml; generalized protocol indicates a 4 hour incubation with test material; no increase in mutation frequency reported; UNACCEPTABLE (single trial, inadequate report - single page plus one table of summary data which contains only "total survival" in percent and "mutation frequency"; no individual plate counts, not total colony counts, no data for growth by days; only generalized protocol not specified for this study - the full report with raw data should be submitted.) JG, 10/28/87

149 - 014 116795 "Mutagenicity Evaluation of Extract of 925981-1 in the Microbial Reverse Mutation Assay by Preincubation Method, " (Jagannath, D.R.; Hazleton Biotechnologies Company, Kensington, MD; Project #: HBC 20988; 5/86). A DMSO extract of 925981-1 was evaluated for mutagenicity at 0 (DMSO), 7, 15, 20, 30, 40, 50 and 100 µl/plate with Aroclor-induced hamster liver metabolic activation (S9 Mix), using *Salmonella typhimurium* strain TA 98. Bacteria were incubated with the test material for 20 minutes before adding agar and plating in triplicate. Tested only with activation. No increase in the number of revertants occurred with 925981-1 treatments. UNACCEPTABLE (Not a FIFRA Guideline study). No adverse effect indicated. These data are supplemental. (Kishiyama & Silva, 5/25/01).

149 - 014 116797 "Mutagenicity Test on an Extract of 917700-5 in the Ames *Salmonella*/Microsome

Reverse Mutation Assay by the Preincubation Method," (Jagannath, D.R.; Hazleton Laboratories America, Inc., Kensington, MD; Project #: HLA 9826-0-401E; 5/8/87). A DMSO extract of 917700-5 was evaluated for mutagenicity at 7, 15, 20, 30, 40, 50, and 100 µl/plate with Aroclor 1254-induced male hamster liver metabolic activation (S9 Mix), using *Salmonella typhimurium* strain TA 98. Bacteria were incubated with the test material for 20 minutes before adding agar and plating in triplicate. Tested only with activation. There was no increase in the number of revertants with the extract of 917700-5 treatments. UNACCEPTABLE (not a FIFRA Guideline study). These data are supplemental. (Kishiyama & Silva, 5/25/01).

149-020 117328A *"In Vivo and In Vitro* Mutagenicity Studies Paraffinic Oil 78-9 70 SUS/100°F," (Hoberman, A.M.; Hazleton, Laboratories Inc., Project Numbers: 596-111, 596-112 & 596-113; 6/19/82). 70 Second Paraffinic Oil (AP #78-9) at concentrations of 40000, 45000, 80000, 160000 and 240000 µg/plate (+/- S9) was assessed for mutagenicity by use of *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 by plate incorporation and 20-minute preincubation assays with triplicate plates per concentration in a single trial. No evidence of mutagenicity with 78-9-70 was observed under study conditions. However, test article insolubility and inability to demonstrate toxicity hindered a full evaluation for mutagenic potential using this system. UNACCEPTABLE. These data are supplemental. (Kishiyama & Silva, 1/22/01).

149 - 020 117328B *"In Vivo and In Vitro* Mutagenicity Studies Paraffinic Oil 78-9 70 SUS/100°F"; Part B: Mouse Lymphoma Forward Mutational Assay," (Hoberman, A.M., Hazleton Laboratories Inc., Project #'s: 596-111, 596-112 & 596-113; 6/19/82). 70 Second Paraffinic Oil (78-9 70) at concentrations ranging from 8,670 to 121, 380 µg/ml (+/- S9 Mix) was used on L5178Y mouse lymphoma cells. **Some 78-9-70 (+S9 Mix) had two-fold increases (non-dose related) in the frequency of mutation**. The results are equivocal; however, because the culture media was saturated with 78-9 70 at all doses. This makes the observed increases (without dose-response) uninterpretable. Not acceptable and not upgradeable (inadequate dose selections, plus missing information) These data are supplemental. (Kishiyama & Silva, 1/24/01).

149 - 021 117329: "Polynuclear Aromatic Analyses and Modified Ames Test on Base Lube Stocks". (Deitch, R., Mobil Oil Corporation Toxicology Division, Study nos.: 61312, 61322, 61332, 61342, and 61352; 9/89). Second Paraffinic Base Stocks 800, 550, 350, 150 and 70 were tested with *Salmonella typhimurium* strain TA98 at 50 µl, 40 µl, 30 µl, 20 µl, 10 µl, 7µl, and 5 µl with metabolic activation from hamster liver, using 8x the usual concentration. No evidence of mutagenicity reported. UNACCEPTABLE (no rationale for dose selection, statistical analyses, analysis of dosing material, GLP and QA sign-off, treatments without metabolic activation; only one *Salmonella typhimurium* strain and some data not legible). No adverse effect indicated. These data are supplemental. (Kishiyama & Silva, 5/2/01).

149 – 020 117324 "The Genotoxic and Carcinogenic Potential of Engine Oils and Highly Refined Lubricating Oils," (McKee, S.C., Przygoda, R.T.; Exxon Biomedical Sciences, Inc., East Millstone, NJ). Three in vitro assays were compared (*Salmonella* and the mouse lymphoma, Syrian hamster embryo (SHE) morphologic transformation assays) to the dermal carcinogenicity of a series of petroleum-derived materials including engine oils and highly refined lubricating oils. One sample of the unused gasoline engine oil was not active in an epidermal carcinogenesis bioassay. This material was also not mutagenic to Salmonella and did not transform SHE cells. Primary components of engine oils are highly refined lubricating oil base stocks. The highly purified fractions tested were not dermal carcinogens, nor were they mutagenic or transforming. Conversely, other materials, including unrefined vacuum ddistillates and solvent extracts of these distillates were both carcinogenic and genotoxic. Thus, results in all *in vitro* and *in vivo* assays correllated. These data are supplemental (no worksheet) and was an abstract only (no

data were presented). M. Silva, 7/17/01.

CHROMOSOME EFFECTS

50667 - 001 037860 "In vitro sister Chromatid Exchange in Chinese Hamster Ovary Cells - Soltrol 130 - Final Report." (Hazleton, 1/13/83) Isoparaffinic hydrocarbons, Soltrol 130, "assumed 100%"; tested in Chinese hamster ovary cells with and without rat liver activation at 0, 0.5, 1.7, 5.0, 17 or 50 mg/ml based on growth inhibition (no data): two hour exposure; scored 50 metaphases per concentration for sister chromatid exchanges; no increase in incidence reported; UNACCEPTABLE (only generalized protocol with a single page specific for this study and one table of summary data - need full report with cytotoxicity data to justify concentrations used. Explanation for including cyclohexane in the table when the solvent was stated to be DMSO.) JG, 10/28/87.

149 - 020 117328C *"In Vivo and In Vitro* Mutagenicity Studies Paraffinic Oil 78-9 70 SUS/100°F," (Hoberman, A.M., Hazleton Laboratories America, Inc.; Project #'s: 596-111, 596-112 & 596-113; 6/19/82). 70 Second Paraffinic Oil (AP #78-9-70) was administered for 5 consecutive days to Sprague-Dawley rats (5/sex/dose) at 0 (corn oil), 500, 1000 and 2000 mg/kg, using bone marrow cells (femurs) to evaluate potential for induction of chromosomal aberrtions. Animals were sacrificed on the day following the final dose. Fifty metaphases per animal were scored. No treatment related effects were observed. This study is not currently acceptable, but is possibly upgradeable upon submission of a QA statement, page 37, rationale for dose selection and analysis of dosing material. No adverse effects. (Kishiyama & Silva, 1/24/01)

DNA DAMAGE

No study submitted

MISCELLANEOUS/OTHER

149-020 117314 "The Carcinogenic Initiating and Promoting Properties of Lightly Refined Paraffinic Oil," (McKee, R.H., Plutnick, R.T., Przygoda, R.T.; Fundamental and Applied Toxicology, **12**:748-756 (1989)). Dermal carcinogenic potential of petroleum-derived liquids is related to polycyclic aromatic hydrocarbon (PAH) content (distill at > 700 °F). Saturated and aromatic fractions of lightly refined paraffinic oil (LRPO: kerosene, diesel fuel, heating oil), or "middle-distillates," (boil at 490-610 °F) have very low concentrations of PAH's and were considered non-carcinogenic. In this study, LRPO and subfractions were tested at 0 (DMSO), 10, 50, 100, 500, 1000, 2000, 5000 and 10000 µg/plate (+/- S9 Mix & +/- Tween 80 solubilization) with *Salmonella typhimurium* strain TA-98. *In vivo* **Initiation:** Groups of 30 CD-1 male mice were treated dermally with DMBA at 10 or 50 µg in 25 µl acetone (1 dose), 150 µl LRPO (divided into saturated and aromatic fractions) or acetone (6x at 25 µl each over 2 weeks); and **Promotion:** TPA (2.5 µg in 25 µl acetone) or LRPO or acetone (25 µl) three times weekly. Mice evaluated for initiating potential were treated 352 days and for promotion, 193 days. There was no *in vitro*-induction of gene mutation with LRPO or subfractions. Therefore, the tumorigenicity of LRPO was not due to low levels of PAHs or to an interation between initiating and promoting constituents. **DMBA/LRPO treated mice had a total of 11 tumors, with a 17% incidence (5/30 mice) which may indicate weak promoter activity.** None of the mice receiving DMBA alone developed tumors. Skin irritation as acanthosis (moderate-severe focal for 10/30 mice/group) and subepidermal inflammatory infiltrate (all LRPO treated mice) may have been responsible for the

promotion effects. Supplemental data. (Kishiyama & Silva, 12/4/00).

149 - 021 117331 "Adaptation of the *Salmonella/*Mammalian Microsome Test to the Determination of the Mutagenic Properties of Mineral Oils," (Hermann, M., Chaude, O., Weill, N., Bedouelle, H., Hofnung, M.; Published in: Mutation Research, 77 (1980) 327 – 339). *Salmonella typhimurium* strain TA 98, " S9 was used in the plate incorporation assay. Two techniques to determine potential mutagenicity of mineral oils have been developed by using benzo[a]pyrene dissolved in white oil as a synthetic reference oil. The dispersal of the compound in aqueous medium with Tween 80 is a simpler and a more generally accepted technique, compared to the extraction of polynuclear aromatic hydrocarbons with DMSO. These new techniques make possible the study of potential mutagenicity for various extracts of mineral oil. Mutagenicity was observed with used crankcase oil and petroleum distillates but to a lesser extent with solvent-refined oils. Results correlated with PAH content but not BP content of oils. Supplemental data. (Kishiyama & Silva, 5/2/01).